SYNOPSIS ON THE PROPOSED AREA OF RESEARCH RELATED TO Ph.D WORK

THEORETICAL STUDIES ON THE MECHANISM OF THE UN-CATALYZED AND METAL CATALYZED SMALL AND MEDIUM SIZE RING FORMING REACTIONS.

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Synopsis of proposed ph.d work

Title:- Theoretical studies on the mechanism of the un-catalyzed and metal catalyzed small and medium size ring forming reactions.

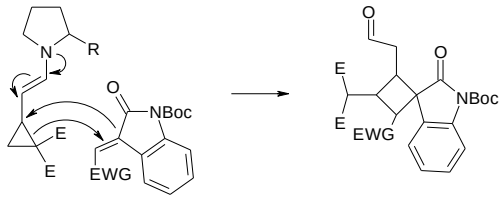
Origin of the research problem:-

Theoretical and experimental chemists are able to do research more efficiently if they have a model for understanding the chemistry. Research on the study of stereoselective organic reactions and its applications for synthesizing different target molecules is probably an important site for illustrations. To rationalize the stereoselectivity for a stereoisomeric product in a stereoselective reaction, it is a common practice to use some models of the possible transition states and work out various interacting forces to determine their stability. Thus, molecular modeling is necessary to determine the actual reaction mechanisms as well as the composition of reaction product of stereoselective reactions.

The chemistry of cyclopropane attracts the attention of several researchers for a long time. When one considers its C-C-C internuclear angles are 60^{o} it has anomalously low strain energy. It is also puzzling that its C-H bond vibrational frequencies resemble olefins much more closely than alkanes. Furthermore cyclopropane undergoes addition reactions in a similar manner to ethylene[1]. Trying to understand and explaining these unusual chemical properties, in addition to describing the bonding scheme in a molecule with such small bond angles, has occupied chemists for years[2].

In this report we have theoretically investigated the mechanism of cyclopropane ring opening reaction of cyclopropane ring by organocatalysis.

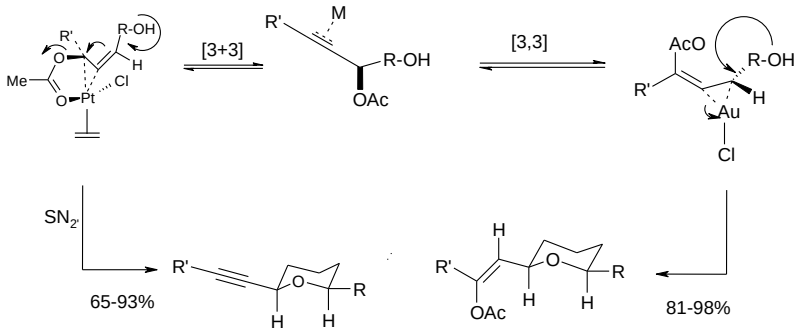
The experimental result as revealed from the report of Jorgensen et.al.[3] shows that cyclopropyl acetaldehyde after condensation with a secondary amino compound can be transformed to an unexpected result (Scheme-1) with highly stereoselective formation of spirocyclobutanes. This process functionalizes cyclopropane ring at one side, which is commonly considered to be an inert portion of the ring. Initiation of the reaction may be considered to occur through a favorable orbital interaction between the π-system of the enamine and the σ*C-C orbital of the cyclopropyl ring. The reaction of Donar–Acceptor cyclopropane is promoted by a lewis acid, which increases their electrophilicity by coordination to the acceptor unit.



Scheme1

In another report under the metal catalyzed category we would like to investigate theoretically the mechanism of Au(I) and Pt(II)- catalyzed cycloetherification.

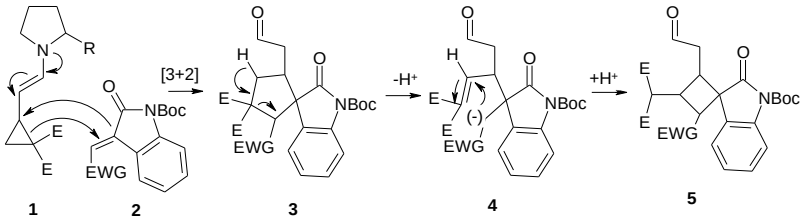
Brabander.*et.al*[4] in their experimental result show that depending on the nature of the metal catalyst, ω-hydroxy propagylic acetates undergoes cycloetherification manifolds to produce functionalized heterocycles in high yields. AuCl catalyzes the formation of oxacyclic enol acetates, where as $[Cl_2Pt(CH_2CH_2)]_2$ (Zeise's dimer) will induce a propagylic substation via S_N2'-type allenic substitution from within a square planar cationic Pt(II) complex (scheme-2).



Scheme-2

Objectives of the work:-

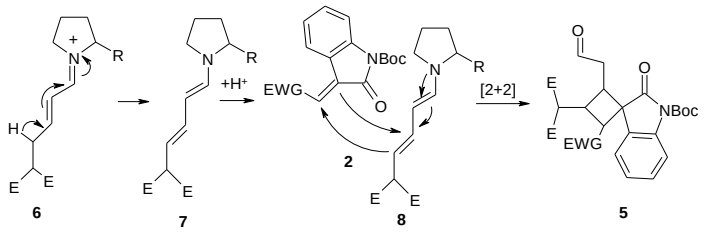
Our objective is to investigate the energetic of two reaction pathways. An initial [3+2]-cycloaddition may take place between the 3-olefinic oxindole **2** and the organocatalytically activated cyclopropane **1**. Subsequently, a ring-contracting rearrangement of the spirocyclopentaneoxindole**3**may take place to form the spirocyclobutaneoxindole product **5** via an initial deprotonating ring opening and generation of **4.**This step is followed by a conjugated addition of the carbanion (Scheme-3). Although ring-contracting rearrangements have previously been a successfully applied strategy in the synthesis of welwitindolinone A isonitrile.[5,6,7]



Scheme-3

Another possible mechanism involves the organocatalytic activation of the cyclopropyl functionality leading to the formation of the iminium-ion intermediate **6** by a ring opening step. From this intermediate, a dienamine **7**can be formed by deprotonation. This dienamine

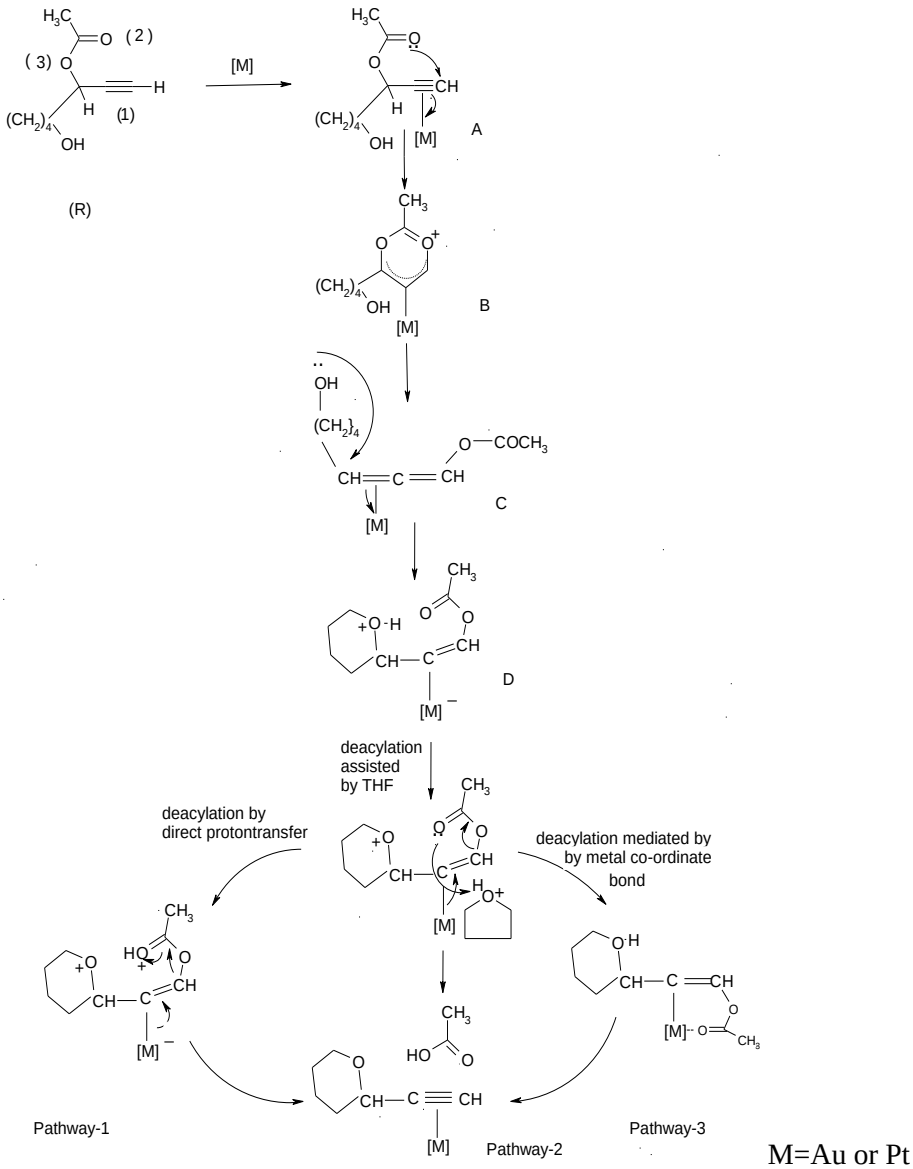
intermediate may then react in a formal [2+2]-cycloaddition with the 3-olefinicoxindole **2** to form the spirocyclobutaneoxindole product **5**(scheme-4).



Scheme-4

In our plan of the metal catalyzed cycloetherification[4] the plausible pathways are summarized in Scheme-5 where **M** indicates the platinum or gold metal centre. All the pathways were considered to start with the formation of the coordinate complex of the reactant **R** with **M.** Three possible sites in the substrate, viz the C ≡C π-system (indicated by 1), the carbonyl oxygen (indicated by 2), and the alcoholic oxygen (indicated by3) of the propagylic ester may be considered as the possible points for co-ordination. However previous literature shows that for a fruitful reaction, the coordinate complex should be formed between the triple bond and the metal centre. The resulting complex undergos a [3+3] sigmatropic shift through a six membered cyclic intermediate **(B)** to generate metal-bound allene complex **(C).** The complex (C) then undergoes a nucleophilic attack by the terminal alcoholic oxygen to the metal bound allene moiety to form a six membered cyclized intermediate **D**. Intermediate **D** may follow three possible pathways (designated as path-1,2 and 3) to form the deacylated cyclic alkyne (P) as the end product. In **pathway-1** the protonated oxygen of the newly formed pyran ring transfer its associated proton to the oxygen atom of the acyl group thus facilitates it to move out from the intermediate. Such proton transfer process in **pathway-2** occurs through the assistance of an external solvent molecule, THF, to converge to a deacylated product. In **pathway-3** a chelate complex between

the metal centre and carbonyl oxygen of the transferred acyl group takes place as the first step. The proton transfer from the newly formed pyran ring deacylates the co-ordinated acyl group to form the product.



Scheme-5

Methodology:-

COMPUTATIONAL METHODS

Methods of calculation:-

For the computational modelling of the proposed project work, Quantum Mechanical (QM) methods will be adopted. The geometry optimization and energy calculation of all the systems will be performed by using Gaussian 09[8] software. For visualizing the output files, some graphics software like gauss view[9] , Molden[10] ,Gabedit[11] or VMD etc will be used.

For most of the cases we will be employed Density Functional Theory (DFT) method for finding out the stationary points. B3LYP hybrid functional and 6-31G* basis set will be used for this purpose. In most of the cases Cartesian Coordinates will be used to optimize the geometry. For optimization of ground state geometry suitable algorithm will be used.

The most important task of this modelling will be the exploration of the potential energy surface (PES) of the molecular assembly involved in the reactions. The potential energy surface is the most complete description of all the conformers, isomers and energetically accessible motions of a molecular system. Most informative stationary points are the minima and the saddle points. Minima on the potential energy surface (PES) correspond to the optimized geometries. The lowest energy minimum is called global minimum. The transition structure between the reactant and product of a reaction is a saddle point. At the stationary point the surface is parallel to the horizontal line corresponding to one geometric parameter or to the plane corresponding to two geometric parameters or to a hyper plane corresponding to more than two geometric parameters. Hence, the first derivative of the potential energy with respect to each geometric parameter is

zero i.e $\delta E/\delta q=0$. However, a minimum is a minimum in all directions, but a saddle point is a maximum along the reaction coordinate and a minimum all other directions. They can be distinguished by the second derivative of energy with respect to the nuclear coordinates. Mathematically it can be written as, at the minimum,$\delta^2E/\delta q^2>0$ for all values of q; And at the saddle point, $\delta^2E/\delta q^2>0$ for all q, except along the reaction coordinate. Along the reaction coordinate,$\delta^2E/\delta q2<0$. A PES can be used to find both the saddle points and the reaction co-ordinates.

Future Prospect:-

Considering all the reported experimentral results it may be stated that the study of the mechanism of reaction pathway of un-catalyzed and metal catalyzed ring forming reactions tells us several features such as: activation energy, stereoselectivity related to the process. We hope that all these works will give successful results and our proposed pathways, through uncatalyzed and catalytic condition, explain all this features. We also believe that the outcome of our theoretical investigations will give a new idea about the reaction mechanism of the small and medium size ring forming reactions.

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